The New England
Journal of Medicine

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Volume 233 SEPTEMBER 13, 1945 Number 11

THE EFFECT OF CHEMOTHERAPY ON THE DURATION OF THE CARRIER STATE FOLLOWING SCARLET FEVER*

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THE utilization of chemoprophylaxis in the control of infections spread by the respiratory tract is a recent development that is gaining ever wider application. In 1939 it was shown that sulfanilamide was effective in preventing streptococcal upper respiratory infections and relapses in rheumatic fever.[1-3] Kuhns et al.[4] found that sulfadiazine, when given prophylactically, diminished meningococcal carrier rates as well as the incidence of meningococcal meningitis. During the course of a scarlet-fever epidemic in a United States naval station, the routine administration of prophylactic doses of sulfadiazine to healthy contacts appeared to be effective in checking its spread.[5]

Conflicting reports have appeared concerning the efficacy of the sulfonamides in preventing complications following upper respiratory infections. Rhoads and Afremow[6] found that sulfanilamide did not reduce the incidence of sequelae in cases of pharyngitis and tonsillitis. Kernan,[7] on the contrary, observed that complications were decreased when patients with tonsillitis were treated with this drug. Quite recently it was observed that sulfadiazine in a solution of ethanolamines (Pickrell's solution) administered as a spray to the nose and throat reduced the frequency of bacterial infections following the common cold.[8] Although Cecil et al.[9] found that the sulfonamides did not alter the course of the uncomplicated "cold," there was some evidence that in certain cases secondary infections were prevented by the oral use of sulfadiazine. Bacteriologic studies revealed a constant reduction in the total number and variety of pathogens cultured from the upper respiratory tract following the administration of 3 gm. of sulfadiazine daily for four days.

The occurrence of two small outbreaks presented an opportunity to study the effect of chemoprophylaxis on the spread of scarlet fever. Although many workers have studied the efficacy of sulfonamides in preventing complications of scarlet fever, little thought has been given to the possibility that treatment of scarlet fever with this group of drugs may reduce the incidence of secondary cases. Among 38 hospitalized cases of scarlet fever, we have observed that 32 patients when discharged from the isolation unit still harbored the identical organism that was present on admission. It is apparent that the problem of late secondary cases is closely linked with the prolonged carrier state that may follow scarlet fever.

Purpose and Method of Study

The purpose of this study was therefore to determine whether chemotherapy reduces the duration of the carrier state in the scarlet-fever cases observed in these two epidemics. At the same time, in an attempt to prevent the possible occurrence of secondary cases among the contacts, exposed persons were given small daily doses of a sulfonamide preparation. Unfortunately, the number of contacts in both epidemics was so small that it was impractical to divide them into two groups, one to receive chemotherapy and the other to remain untreated. Nevertheless, interest was centered on the period of communicability of the treated and untreated cases.

Cases that occurred in the first outbreak were treated with sulfamerazine. The duration of the carrier state of these cases was compared with that of cases occurring in the second outbreak, all but 2 of which received no chemotherapy during the acute stage of the disease. Contacts in the first epidemic received small daily doses of sulfamerazine, whereas those in the second were treated with daily applications of Pickrell's solution as a spray.

To evaluate as accurately as possible the immunity status of persons carrying Lancefield Group A streptococci in the nose and throat, the Dick test was performed on all contacts. Serial nose and throat cultures were utilized to determine the duration of the carrier state in cases and contacts.

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In addition to the investigation of the outbreaks, further studies on the duration of the convalescent carrier state were made by serial nose and throat cultures of sporadic cases admitted to two contagious hospitals. In one of these institutions, in which chemotherapy was utilized only for severe cases, we observed 13 patients treated with sulfadiazine and 26 untreated cases. The majority of the sulfadiazine-treated patients were from six to twelve years of age and were given 0.5 gm. of the drug every four hours for seven to ten days.

In the second institution where scarlet-fever patients had been treated routinely with sulfathiazole, three groups of cases were studied. One group (12 cases) received no chemotherapy; the second (16 cases) received sulfathiazole; and the third (13 cases) received Pickrell's solution as a spray. Children above the age of six received 0.5 gm. of sulfathiazole five times daily for five to seven days. The Pickrell's solution was administered as a spray to the nose and throat four times daily for twenty-one days. The observation period varied from five to nine weeks.

Bacteriology

Nose and throat swabs were streaked on 5 per cent horse-blood agar and cultured in beef-heart infusion broth. All mediums contained 0.005 per cent para-aminobenzoic acid.[10] Plates were examined after eighteen to twenty-four hours incubation at 37°C. and typical beta-hemolytic colonies were fished to beef-heart infusion broth. If hemolytic streptococci were not isolated from the original plate, the broth culture of the swab was appropriately diluted and streaked on blood agar. All Lancefield[11] Group A hemolytic streptococci were typed by the slide agglutination method described by Griffith.[12] Agglutination of granular or self-agglutinating cultures was facilitated by digestion with trypsin, as described by Allison.[13]

The strains isolated from the 14 cases — 10 of scarlet fever and 4 of sore throat — and 16 contacts in Outbreak A agglutinated with type-specific rabbit antiserum prepared against Griffith's Strain 130 (Type 1). These streptococci grew as glossy colonies. The strains isolated from the 11 cases and 9 contacts in Outbreak B agglutinated with type-specific rabbit antiserum prepared against Griffith's Strain Franklin (Type 5). These streptococci grew as typical matt colonies. Both the Griffith Type 1 and Type 5 strains produced a toxin homologous with that of Strain N. Y. 5, as determined by toxin-antitoxin neutralization tests in rabbits.[14]*

Epidemiology

Outbreak A

The first outbreak occurred in a small country orphanage with 31 inmates, 26 of which were children four to fifteen years of age. Several of them attended local schools where scarlet fever was prevalent. One of these, a nine-year-old boy, developed scarlet fever late in September, 1943. The original patient made an uneventful recovery, but 10 cases of scarlet fever and 4 of streptococcal sore throat occurred in the orphanage from November 7 to 16. The distribution of cases according to the day of onset is shown in Figure 1. Such a distribution suggests a common source, but this could not be established by the investigation.

Nose and throat cultures of cases and contacts revealed a Group A, Type 1, streptococcus as the causative agent. This organism was recovered in the first series of cultures from 7 cases and 15 contacts, indicating widespread dissemination of the causative organism among the inmates over a comparatively short interval of time. It is noteworthy that of 15 contacts who harbored the causative organism in the nose or throat, 10, all children, had positive Dick tests (Table 1).

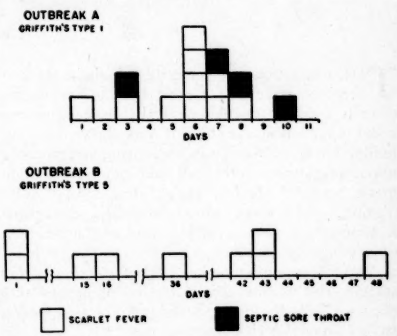

FIGURE 1. *Day of Onset of Scarlet Fever and Sore Throat. Two missed cases are not included.*

The first cultures were taken after the scarlet-fever cases had received 1 gm. of sulfamerazine daily for five days. When it was discovered that a large proportion of the susceptible subjects (with positive Dick tests) harbored the etiologic agent, it was decided to administer prophylactic doses of a sulfonamide. Half a gram of sulfamerazine was administered once daily to all contacts for ten days. Subsequently, contacts with positive Dick tests were treated for an additional five days. Cultures taken at this time revealed that 6 persons — 3 patients and 3 contacts — still harbored a Type 1 streptococcus. Two of the patients had developed a minor complication — one a cervical adenitis and the other a nasal discharge. These 6 persons were then treated with a 2.5 per cent solution of sulfadiazine (Pickrell's solution) as a spray to the nose

*These toxins were prepared by Dr. Geoffrey Edsall, acting director of the Division of Biologic Laboratories, Massachusetts Department of Public Health.

and throat, administered five times daily for five days. Cultures taken after the spray treatment (twenty-one days after chemoprophylaxis was begun) revealed that Type 1 streptococci had disappeared from the entire group (Table 1). A carrier of Type 1 streptococci was disclosed in the final series of cultures two weeks later. Dick tests performed at that time revealed that a reversal from positive to the beginning of the study are summarized in Figure 2, which also records the results of Dick tests and nose and throat cultures of the contacts. It was found that 11 healthy persons, including the teacher, carried Type 5 streptococci in the nose or throat. Of 14 contacts with positive Dick tests, 5 harbored the causative organism.

Study of air-flow currents* revealed that 20 per

TABLE 1. *Cultural and Dick-Test Status of Cases and Contacts in Outbreak A.*

Case No.	Age	Diagnosis	Dick Tests*		Type of Hemolytic Streptococcus					
			Primary	Secondary	First week†	Second week	Third week	Fourth week‡	Fifth week	Seventh week
	yr.									
1	10	Scarlet fever	+	−	1	1	1	1	0	19§
2	13	Scarlet fever	+	+	1	0	0	0	0	19§
3	13	Scarlet fever	+	−	1	1	1	1	0	0
4	4	Scarlet fever	+	−	1	1	0	0	0	0
5	4	Scarlet fever	+	−	0	1	0	0	0	1
6	6	Scarlet fever	+	−	0	0	0	0	0	0
7	6	Scarlet fever	+	−	0	0	0	0	0	0
8	3	Scarlet fever	+	−	0	1	1	1	0	0
9	5	Scarlet fever	+	−	0	0	0	0	0	0
10	8	Scarlet fever	+	−	1	1	1	0	0	0
11	13	Sore throat	+	+	1	1	1	0	0	0
12	13	Sore throat	+	+	1	1	0	0	0	6
13	7	Sore throat	+	−	0	0	0	0	0	0
14	12	Sore throat	−	−	0	1	1	0	0	0
15	12	Contact	+	+	1	1	1	0	0	0
16	13	Contact	−	−	1	0	0	0	0	0
17	10	Contact	+	+	1	0	0	0	0	0
18	10	Contact	+	+	1	1	1	0	0	0
19	15	Contact	+	+	1	0	0	0	0	0
20	15	Contact	+	+	1	0	0	1	0	0
21	12	Contact	+	−	1	1	0	0	0	0
22	13	Contact	−	−	1	0	0	0	0	0
23	11	Contact	+	+	1	0	0	0	19§	0
24	9	Contact	+	+	1	0	1	1	0	0
25	12	Contact	+	+	1	0	0	0	0	0
26	14	Contact	+	+	1	1	1	0	0	0
27	56	Contact	−	−	0	0	0	0	0	0
28	67	Contact	−	−	?	1	0	0	0	0
29	58	Contact	−	−	1	1	0	0	0	?
30	60	Contact	−	−	1	1	1	1	?	?
31	62	Contact	−	−	1	0	0	0	0	2

*Primary Dick tests done after onset of the first cases.
†Patients had had oral drug for five days before the first series of cultures.
‡First cultures after contacts treated for fifteen days with sulfamerazine (0.5 gm. daily).
§Weak cross agglutination with Types 4, 24, 26 and 29.

negative had occurred in 1 of the contacts and in 10 of the patients (Table 1).

Outbreak B

The second outbreak occurred among 33 fifth-grade children in a single room of an elementary school with a total population of 495 children distributed among fourteen schoolrooms. Scarlet fever was reported from the involved room only. A total of 9 cases of scarlet fever occurred in this room from December 6, 1943, to January 24, 1944. Two additional cases were revealed during the course of the epidemiologic investigation. The dates of onset (Fig. 1) suggest transmission from patient to patient or from carrier to patient.

Nose and throat cultures obtained from all 11 cases revealed a Group A, Type 5, streptococcus as the etiologic agent. The findings in the room at cent of the air within the schoolroom was being recirculated by means of a unit ventilator. Streptococci were recovered from six of thirty-six blood agar plates that had been exposed for twenty-four hours on desks vacated by children who had developed scarlet fever, and from two cultures taken from dust that had collected on the ventilator fan. Of these eight cultures, two showed Type 5 streptococci. Of twenty blood agar plates exposed in an adjacent room where no scarlet-fever cases had occurred, hemolytic streptococci were recovered from three; none of these were Type 5.

When it was discovered that a large proportion of the contacts were carrying a Type 5 streptococcus, chemoprophylaxis was begun in an attempt to protect the susceptibles. All children remaining

*We are indebted to Mr. C. P. Yaglou, of the Harvard School of Public Health, for the studies of ventilation.

in the room received 2½ per cent sulfadiazine in ethanolamine solution as a spray daily, once during the morning and once during the afternoon. Included in this group were 4 convalescent scarlet-fever cases, all with cultures positive for Type 5 streptococci. After seven days of spray treatment, a second series of cultures revealed that 4 contacts and 3 convalescent patients were still carrying a Type 5 streptococcus. During the second week, spray treatment was restricted to those children who had positive Dick tests in addition to those whose cultures were still positive for Type 5 streptococci. Table 2 indicates the number of carriers before and after spray treatment. It will be seen that after the second week only 1 healthy contact had a positive culture for the etiologic organism.

At the time that the last 4 scarlet-fever patients had been released from isolation and were about to return to school. Of these, 1, who had received chemotherapy early in the course of the illness, had negative cultures. The remaining 3 were still carrying Type 5 streptococci. To eliminate as many potential sources of infection as possible, the convalescent patients with positive cultures were given 1 gm. of sulfadiazine daily for four days. At the end of that period and one week later the cultures were negative. Subsequent cultures of the entire group after two weeks and again after four weeks revealed the presence of Type 5 streptococci in the nose and throat of 4 of the convalescent patients. No new infections appeared in the schoolroom.

Nose and throat cultures were taken from the family contacts of several of the scarlet-fever patients. Of 23 contacts examined (Fig. 3), 13 had cultures positive for Type 5 streptococci. Five secondary cases, in none of which the patients attended school, occurred among the family contacts of the 11 primary-infection cases. Type 5 streptococci were recovered from each of these secondary cases.

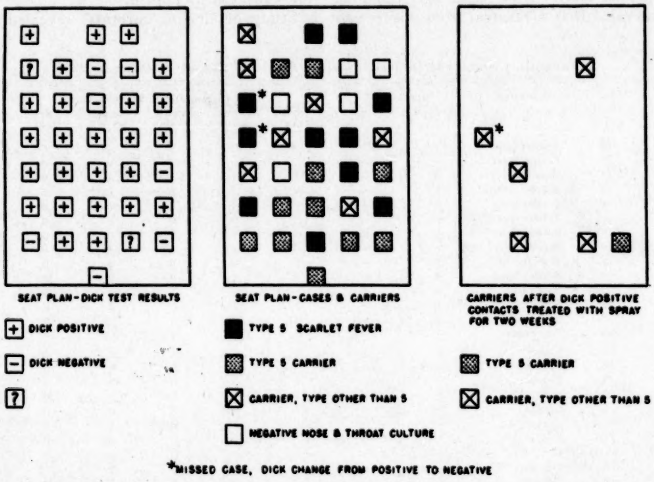
SEAT PLAN - DICK TEST RESULTS
DICK POSITIVE
DICK NEGATIVE
SEAT PLAN - CASES & CARRIERS
TYPE 5 SCARLET FEVER
TYPE 5 CARRIER
CARRIER, TYPE OTHER THAN 5
NEGATIVE NOSE & THROAT CULTURE
CARRIERS AFTER DICK POSITIVE CONTACTS TREATED WITH SPRAY FOR TWO WEEKS
TYPE 5 CARRIER
CARRIER, TYPE OTHER THAN 5
*MISSED CASE, DICK CHANGE FROM POSITIVE TO NEGATIVE

FIGURE 2. *Data on an Outbreak of Scarlet Fever among the Children in a Schoolroom.*

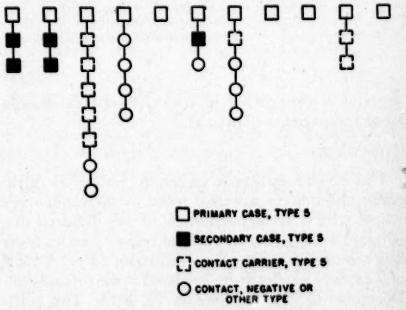

FIGURE 3. *Diagram Showing the Spread of Hemolytic Streptococci among Scarlet-Fever Contacts.*

During the course of this outbreak a total of 25 cases of scarlet fever had occurred in the entire com-

munity. Of these, 16 (64 per cent) were associated with the schoolroom outbreak. Type 5 streptococci were recovered from a single sporadic case. The remaining cases were caused by one of several other serologic types — Types 2, 1 and 6 in order of frequency.

Effect of Chemotherapy

Cases in Outbreaks

The duration of the postscarlatinal carrier state patient who had received chemotherapy lost the causative organism before the second week of the illness. A second had negative cultures after the fifth week. Although subsequent cultures did not reveal the etiologic organism for an additional four weeks, there was a reappearance of the same type of streptococcus in the fifth week (the tenth week after onset).

Cases 6, 7, 8 and 9 in Outbreak B are worthy of mention. These patients had received no sulfa-

Table 2. *Cultural and Dick-Test Status of Cases and Contacts in Outbreak B.*

Case No.	Diagnosis	Primary Dick Test*	Type of Hemolytic Streptococcus									
			First week	Second week	Third week†	Fourth week	Fifth week	Sixth week	Seventh week	Eighth week	Tenth week	Eleventh week
1	Scarlet fever	+	5	5	5	5	5	0	0	?	?	?
2	Scarlet fever	+	5	5	5	5	5	2	0	0	5	0
3	Scarlet fever	+	5	5	5	5	5	0	2	2	0	2
4	Scarlet fever	+	5	5	5	5	5	0	0	0	0	0
5	Scarlet fever	+	5	5	5	5	5	0	0	0	5	0
6	Scarlet fever	+	5	5	5	5	5	5	0	0	0	0
7	Scarlet fever	+	5	5	5	5	5	0	17‡	0	17‡	0
8	Scarlet fever	+	5	5	5	5	5	0	0	0	0	0
9	Scarlet fever	+	5	5	5	5	5	19§	19§	19§	5	5
10	Scarlet fever	+	5	0	1	1	0	1	1	0	1	0
11	Scarlet fever	+	5	5	5	5	5	0	17‡	17‡	17‡	5
12 (teacher)	Contact	−	5	5	0	0	0	0	0	0	0	0
13	Contact	−	5	0	0	19§	0	0	0	0	0	
14	Contact	+	0	0	19§	0	0	0	0	0	0	
15	Contact	+	0	0	0	0	19§	0	0	0	0	
16	Contact	+	5	0	0	0	0	0	0	0	19§	
17	Contact	+	19§	0	0	?	?	0	0	0	0	
18	Contact	+	0	0	0	0	?	0	0	0	0	
19	Contact	+	1	1	0	0	0	0	0	19§	0	
20	Contact	?	5	5	8	8	0	2	2	2	0	
21	Contact	+	5	0	0	0	0	0	0	0	0	
22	Contact	+	2	2	0	2	2	0	0	0	0	
23	Contact	+	0	1	0	0	0	0	0	0	0	
24	Contact	+	5	5	0	1	1	2	2	2	0	
25	Contact	+	5	0	0	0	0	?	?	0	0	
26	Contact	+	5	19§	0	19§	0	8	8	0	0	
27	Contact	−	5	0	0	19§	0	?	?	0	0	
28	Contact	+	0	0	0	0	0	?	0	0	0	
29	Contact	+	0	0	1	0	0	?	0	0	0	
30	Contact	?	19§	0	0	2	0	0	0	0	0	
31	Contact	−	5	0	19§	19§	0	0	0	0	0	
32	Contact	−	8	0	0	19§	0	0	0	0	0	
33	Contact	−	19§	0	19§	0	0	0	0	0	0	
34	Contact	−	5	5	5	0	0	0	0	0	0	

*Secondary Dick tests could not be done.

†First cultures after contacts treated for fourteen days with Pickrell's solution twice daily.

‡Weak cross agglutination with Type 23.

§Weak cross agglutination with Types 4, 24, 26 and 29.

for the cases occurring in both epidemics showed striking differences.

In Outbreak A the average duration of positive cultures for the sulfadiazine-treated cases was less than two weeks. Nose and throat cultures of 6 cases were consistently negative after the third week. In 1 case there was a reappearance of the causative organism after cultures had been negative for four weeks.

The average duration of the convalescent carrier state in Outbreak B was at least eight weeks. One diazine preparation during their acute illness. Following the administration of 1 gm. of sulfadiazine daily for four days, in the fifth week after onset cultures promptly became negative for Type 5 streptococci. In 3 cases, other types of streptococci not identified with this outbreak replaced the Type 5 streptococcus. Here again, subsequent cultures of 1 of these patients disclosed a reappearance of the etiologic organism after a four-week interval during which it had not been demonstrable.

Sporadic Cases

Studies of sporadic scarlet-fever cases revealed similar results (Table 3). Nose and throat cultures of 32 (84 per cent) of 38 untreated cases showed at the time of discharge the identical organism that had been present on admission. However, 10 (62 per cent) of 16 sulfathiazole-treated patients had negative cultures after the third week of illness, and 9 (69 per cent) of 13 sulfadiazine-treated ones had negative cultures after the same period of time. Pickrell's solution utilized as a spray in 13 cases produced negative cultures in 10 (77 per cent) at the conclusion of the three-week isolation period.

Although all three chemotherapeutic agents were equally efficacious in reducing the number of patients carrying the causative organism, subsequent cultures revealed that in a considerable proportion there was a reappearance of the initially isolated streptococcus (Table 3). In 5 (50 per cent), of 10 sulfathiazole-treated cases, such a reappearance occurred at intervals ranging from one to five weeks after the cultures had become negative. Similarly, in 5 (55 per cent), of 9 patients who had negative cultures after treatment with sulfadiazine there was a reappearance of the etiologic streptococcus. Only 3 of the patients who had been sprayed with Pickrell's solution were studied after discharge from the isolation hospital. Reappearance of the causative organism was observed in 2 of these.

TABLE 3. *Effect of Chemotherapy on the Streptococcus-Carrier State Following Scarlet Fever.*

DRUGS	NO. OF CASES	TYPES OF STREPTOCOCCI ISOLATED*	NO. OF CASES WITH POSITIVE THROAT CULTURES			CASES WITH NEGATIVE THROAT CULTURES ON DISCHARGE		CASES IN WHICH ORIGINAL TYPE REAPPEARED 1 TO 5 WEEKS LATER	
			FIRST WEEK	SECOND WEEK	THIRD WEEK	NO.	PERCENTAGE	NO.	PERCENTAGE
Sulfathiazole	16†	1, 2, 19, 17, 8, 6	12	11	6	10	63	5	50
Sulfadiazine	13	2, 1, 8, 6, 5	13	6	4	9	69	5	80
Pickrell's solution	13	2, 6, 8, 17, 1	13	12	3	10	77	2‡	67
None	38	2, 1, 6, 8, 19	37	32	32	6	16	3	50

*In order of frequency.

†Hemolytic streptococci not isolated from 1 case during the period of isolation.

‡Of 3 cases studied.

DISCUSSION

In both outbreaks the etiologic agent appeared to be successfully eliminated from the respiratory tracts of the temporary carriers. Whether the outbreaks were checked by this method is a matter of conjecture. Although a large proportion of the contacts had positive Dick tests, it was impossible to say that these persons were in addition susceptible to the streptococcus itself.

In a study of this type, temporary carriers must be differentiated from convalescent carriers. It was found that although sulfadiazine spray was adequate for the treatment of the healthy carrier, it did not eliminate streptococci from the nose and throat of the convalescent carrier.

Experience with several epidemics in schoolrooms suggests that multiple cases of scarlet fever due to a single type of hemolytic streptococcus are by no means infrequent.[13] Frequently, investigation of contacts during these epidemics reveals the presence of chronic hemolytic-streptococcus carriers, some of whom are found to be either unrecognized cases or convalescent carriers who have returned to school following the expiration of the usual quarantine period.

In the epidemiology of scarlet fever, missed cases and convalescent carriers are far more important as sources of infection than is generally believed. The customary streptococcus-carrier survey does not attempt to differentiate the convalescent case and the healthy carrier. Such surveys will be more useful when an attempt is made to explain the presence of streptococci in the upper respiratory tract by utilizing all available bacteriologic, clinical and epidemiologic knowledge.

Family studies suggest that children who acquire scarlet fever in school convey the infecting organism into the home, where it is dispersed among the contacts, a proportion of whom may develop scarlet fever or some other streptococcal infection.[15] Also, in family units the carrier rate rises as a result of the introduction of a specific organism into the group by a scarlet-fever patient. Similar observations have been made during the course of institutional outbreaks of streptococcal infection.[16] This factor may account for the high healthy-carrier rates associated with the types of streptococci that are causing scarlet fever in a community.

The frequent occurrence of late secondary cases among family contacts on the return to the home of patients cared for in hospitals is a well known fact. Similarly, in the schoolroom outbreak it was shown that with one exception each of the untreated patients who had returned to school still harbored the incriminated streptococcus in the nose and throat at the expiration of the three-week quarantine period.

Our observations suggest that the administration of sulfathiazole or sulfadiazine to scarlet-fever patients results in the development of a temporary period of so-called "cultural latency," during which the causative organism cannot be isolated from the mucous membranes of the nose and throat. After an interval of one to five weeks, however, there is a reappearance in the cultures of the streptococcus that had been isolated earlier in the course of the infection. In seeking an explanation for the observed period of "cultural latency," it may be pointed out that the fundamental mode of action of the sulfonamides appears to be bacteriostatic rather than bacteriocidal.[17]

The question arises whether this period of latency has any effect on the incidence of late secondary cases. Some data concerning this point were available at the contagious hospital where the sulfathiazole-treated cases had been studied. At this hospital 455 cases of scarlet fever had been treated routinely with sulfathiazole over a period of two years — 1942 and 1943. Examination of the hospital and board-of-health records revealed that following discharge of the primary cases from the isolation unit, 25 secondary cases — an incidence of 5.4 per cent — had occurred among the family contacts. From 1939 to 1941, inclusive, following the discharge of 398 hospitalized patients who had received no chemotherapy, 28 secondary cases — an incidence of 7 per cent — were reported among the family contacts.

The interval between the time of discharge of the primary case and the occurrence of the first case of secondary infection was established for each of the two groups. The average interval was 9.2 days for the treated cases and 12.6 days for the untreated ones. From the standpoint of the incidence of secondary cases and of the interval between the discharge of the primary case and the occurrence of the first secondary infection, there was no significant statistical difference between the two groups.*

These observations indicate that the period of "cultural latency" has little effect on the spread of scarlet fever. Additional studies have been undertaken to ascertain the effect of chemotherapy on a larger number of cases. The results of study of untreated cases emphasize the arbitrary nature of the isolation period in scarlet fever. Since the great majority of patients harbor the etiologic organism at the time of discharge from the isolation hospital, it is apparent that the customary three-week isolation period does not accomplish its purpose.

Although it has been demonstrated that the sulfonamides are of therapeutic value, there is little or no evidence that the routine use of chemotherapy has any effect on the incidence of late secondary cases. In this connection, the problems of drug sensitivity and drug fastness merit careful consideration. It must be borne in mind that the sulfadiazine drugs have been most effective in the treatment of the fatal complications of scarlet fever. It would be unfortunate if their value for these secondary infections were impaired by the development of drug-resistant strains. From the point of view of controlling the spread of scarlet fever, there appears to be little justification for the routine treatment of patients with the sulfonamides.

*Statistical significance is assumed where comparisons indicate more than twice the *sigma* of the difference of the rates.

Summary

The epidemiologic investigation of two small outbreaks of scarlet fever, one occurring in an orphanage and due to a Type 1 streptococcus, and the other occurring in a schoolroom and due to a Type 5 streptococcus, presented an opportunity to study the effect of chemotherapy on temporary and convalescent carriers.

In both epidemics the utilization of small daily doses of a sulfonamide preparation — sulfamerazine in the first instance and sulfadiazine (Pickrell's solution) in the other — apparently reduced to a minimum the number of persons carrying the incriminated organism.

Studies among the families of children who acquired scarlet fever in the schoolroom outbreak revealed a spread of the causative organism to a large proportion of the family contacts, with the occurrence of several secondary cases.

A study of a group of untreated scarlet-fever patients showed that when discharged from isolation hospitals the majority carried the same type of streptococcus that was present on admission.

A large proportion of scarlet-fever cases treated with certain of the sulfonamides developed a temporary period of "cultural latency." In approximately half these cases, however, the original streptococcus reappeared in the cultures after an interval of one to five weeks.

A study of sulfathiazole-treated cases suggests that the period of "cultural latency" has no effect on the incidence of late secondary cases.

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HODGKIN'S DISEASE*

Report of a Case of the Mediastinal Type with Leukopenia and Terminal Atelectasis

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SINCE Hodgkin's[1] original description in 1832 of the disease known by his name, many papers have appeared in the medical literature that attempt to clarify both the etiology and pathology as well as the symptomatology of this illness.

So far as the etiology is concerned, the cause of the disease still remains unknown, although two main theories have been put forward to explain its origin.[2] The first holds that the changes in the lymphoid tissues are the result of an infection, the disease thus being a specific infective granuloma of unknown origin. The second theory, on the other hand, considers the alterations in the lymph nodes as neoplastic, thus placing the disease in the category of true neoplasms. The pleomorphism of the microscopic picture, consisting of necrosis with subsequent fibrosis, suggests an inflammatory lesion, whereas the local spread and the uniformly fatal outcome of the disease are characteristic of malignancy. The theory that Hodgkin's disease represents a special form of tuberculosis has been almost entirely disregarded.

Several pathological classifications have appeared, the most recent one, by Jackson and Parker,[3] dividing the disease into three types: paragranuloma, granuloma and sarcoma. This division was made on the basis of two features, namely the presence in each of the so-called "Reed-Sternberg" cells and the transformation, in the course of time, of one type of the disease into another. According to these authors, Hodgkin's paragranuloma bears little or no resemblance to a true tumor, either in its histologic picture or its clinical course, but because of the complete lack of invasiveness, the lymphocytic infiltration, the often scattered, isolated Reed-Sternberg cells and the comparatively benign course, it is considered an infectious process. The same holds true for Hodgkin's granuloma, in which, according to these authors, the frequently scattered, isolated Reed-Sternberg cells, viewed from the pathological standpoint, and the irregular bouts of fever, the marked anemia in absence of bleeding or widespread invasion of the marrow, the polymorphonuclear leukocytosis and the prominent and persistent tachycardia from the clinical point of view are more characteristic of an infectious process than of a tumor. Hodgkin's sarcoma, however, is considered by Jackson and Parker as a true neoplasm. This opinion is based on the uniformity of the cellular constituents, the aggressive, invasive nature of the process, the extremely short duration of life and the not infrequent finding of a large destructive tumor with comparatively few metastases.

So far as the symptomatology is concerned, great difficulties were encountered in dividing the disease into different types, because of the wide scope of the illness and its numerous diverse, protean symptoms. Most authors still accept Ziegler's[4] plan, which divided the disease clinically into nine forms — acute, localized, general, mediastinal, larval or abdominal, splenomegalic, osteoperiostitic, atypical (gastrointestinal — Mikulicz's disease) and mycosis fungoides. It is beyond the scope of this paper to discuss all these forms, but it should be noted that, in spite of Ziegler's classification, there is often a clinical transformation from one of these types into another.

The following case is reported because of its unusual combination of clinical symptoms and the diagnostic difficulties it presented.

C. G., a 28-year-old man, was admitted with the chief complaint of severe vomiting of 2 weeks' duration. Two weeks prior to admission the patient started to vomit 2 hours after taking food and also experienced considerable midepigastric pain. There was also marked weight loss during this period. When admitted to the hospital he presented symptoms of partial intestinal obstruction and marked dehydration.

The past history revealed that the patient had been treated for peptic ulcers for the last 5 years. This type of treatment was undertaken on the basis of the clinical symptoms, which were fairly typical of a peptic ulcer, although repeated gastrointestinal x-ray studies failed to show any evidence of ulcer.

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The regime consisted of a moderate Sippy diet with the addition of alkali, antispasmodics and sedatives. The patient carried out this regime fairly conscientiously, and up until the beginning of the present illness showed no acute symptoms related to the gastrointestinal tract. A complete chest examination, including x-ray films, which was done 1 year before admission, was entirely negative. Six months prior to admission he was hospitalized for 2 weeks for a sprain in the lumbar spine, from which he made a complete and uneventful recovery. Otherwise the past history was uneventful.

The patient's father died of a leukemic condition, the exact nature of which could not be determined. The patient was married and had five children, all of whom were in good health. He had been working as a dispatcher in a war plant for over five years and had never been exposed to any chemicals, such as benzol.

Physical examination on admission showed a markedly dehydrated, poorly nourished man, presenting a clinical picture of partial intestinal obstruction. There was evidence of recent weight loss. Except for some tenderness in the right upper quadrant of the abdomen, the examination was negative. No masses were felt, and there was no enlargement of the liver or spleen, nor were there any palpable lymph nodes.

The urine was negative and had a specific gravity of 1.014. The red-cell count was 3,960,000 and the hemoglobin 65 per cent. The white-cell count was 3100, with 51 per cent polymorphonuclear leukocytes, 47 per cent lymphocytes and 2 per cent eosinophils. A slight polychromasia with anisocytosis was noted. A blood Hinton test was negative. The sedimentation rate was 23 mm. in 1 hr. (Wintrobe method). A blood culture was negative. The icteric index was 5.

A second blood examination, made 10 days after admission, revealed the red-cell count and the hemoglobin to be about the same as on admission, but the white-cell count had increased to 4700. The differential count was approximately the same as on admission. The reticulocyte count was 1.8 per cent, and the blood platelets numbered 350,000. A blood culture was again negative, and the sedimentation rate had decreased to 12 mm. in 1 hr. A gastric analysis showed a faint trace of combined hydrochloric acid but no free hydrochloric acid in the fasting specimen. After histamine injection a faint trace of free hydrochloric acid appeared, but not enough for exact values to be ascertained. Daily stool examinations for occult blood revealed positive findings on four occasions and negative values on one. Agglutination tests for typhoid, paratyphoid and undulant fever were negative. The total serum protein was 7.2 gm. per 100 cc., the albumin fraction being 4.5 gm., and the globulin fraction 2.7 gm. The urine was negative for Bence-Jones proteins.

One month after admission the white-cell count began to show abnormal values in the form of a definite leukopenia, ranging between 975 and 1700 cells, as determined by daily examinations. The differential count showed a neutrophilia, with lymphocytosis on several occasions, but at no time an eosinophilia. On two smears a large number of metamyelocytes and a few myelocytes were found, in addition to many degenerating white cells and basophilic stippling of the red cells. There were also moderate hypochromia, anisocytosis and polychromasia. Except for these two occasions, however, the differential count showed normal values relatively, in spite of the marked leukopenia. The red-cell count during this period varied between 3,000,000 and 3,500,000, and the hemoglobin between 55 and 65 per cent. The reticulocyte count varied between 3.8 and 9.4 per cent, probably as a response to liver therapy. The sedimentation rate ranged between 12 and 20 mm. in 1 hour, and the total protein values remained the same — 7.2 gm. per 100 cc. The gastric analysis was repeated and again showed no free hydrochloric acid on the fasting specimen, but a slight trace appeared after histamine injection. The icteric index was again 5. A blood culture was negative for the third time. A sternal-marrow puncture on two occasions showed entirely normal smears, but microscopical examination of the bony tissue of the marrow showed definite atrophy and fibrosis. Repeated urinalyses were negative except for slight traces of albumin and bacteria in the sediment. Sputum examination was negative.

About 1 week before the patient's death, the white-cell count increased slightly but steadily, finally reaching values between 2500 and 3000, but the differential count remained the same. At the same time, the red-cell count dropped sharply until it reached 1,100,000. The hemoglobin also decreased gradually to 30 per cent. The platelet count, however, remained the same, as did all the other laboratory findings.

An electrocardiogram was negative, except for evidence of slight myocardial damage.

Two complete gastrointestinal series, including a barium enema, were performed 3 months apart, and both were negative. A gall-bladder series (Graham-Cole test) was negative. A flat plate of the abdomen and an intravenous pyelogram were negative. Complete x-ray examination of the long bones, skull, sternum and spine revealed entirely normal findings. Several chest x-ray films were taken, and up to 2 weeks of death were negative; at that time the chest plate for the first time showed complete consolidation of the right base involving the middle and lower lobes. A diagnosis of lobar pneumonia was reported by the roentgenologist. An x-ray film of the chest taken 5 days later showed complete consolidation of the entire right lung. The left lung was clear, and the heart was not displaced. A diagnosis of pneumonia and pleurisy with effusion was made. Another chest film taken 5 days later showed complete opacity of the right side, with no displacement of the heart. A slight increase of lung markings on the left was also reported.

On admission the patient presented the clinical picture of partial intestinal obstruction. He was unable to retain food and complained of severe cramplike pain in the midepigastric region. Following the subsidence of the obstruction he was able to retain a soft diet, but the midepigastric pain continued to be present 1 to 1½ hours after food intake. He also lost weight gradually. There was no fever.

Physical examination 3 weeks after admission revealed marked tenderness and rigidity in the right upper quadrant of the abdomen; the liver was palpable 2 fingerbreadths below the right costal margin. No lymphadenopathy, splenomegaly or tenderness over the splenic region was found, but there was some tenderness on palpation over the flat bones, especially over the sternum. The prostate was not enlarged, tender or nodular. Neurologic examination showed hypoactive tendon reflexes and normal superficial reflexes. There were no sensory disturbances, and the vibration sense was normal.

The patient's condition remained practically unchanged during the 1st month of hospital stay, but he then began to lose ground, slowly but steadily. He started to run a low-grade remittent type of fever, which persisted for 3 weeks, when the temperature finally rose to 104°F. and became sharply intermittent. He complained of severe headaches and again started to vomit. He became extremely weak, and the tenderness over the flat bones, especially over the sternum, continued to increase in severity. On one occasion the spleen appeared to be palpable on deep inspiration and there was marked tenderness over the splenic region, which persisted until death. At no time, however, were there any palpable lymph nodes. The patient's general condition rapidly deteriorated and he lost markedly in strength and weight.

Two weeks prior to death, the patient suddenly developed an increasingly severe cough, productive of a small quantity of white mucus; associated with this was bilateral wheezing, especially marked over the right side of the chest. In spite of the x-ray report of lobar pneumonia, a clinical diagnosis of obstruction of the right lower main bronchus producing atelectasis of the right lower and middle lobes was made. Three days later there was a complete absence of breath sounds over the right lung, with some expiratory wheezing rales on the left side. Clinically there was slight dyspnea and cyanosis, and the cough decreased in severity. This condition continued for 1 week, when the dyspnea markedly increased and the patient began to expectorate large amounts of thick, greenish mucus. Chest examination revealed many expiratory wheezing rales in both lungs and moist bubbling rales at both bases. He then developed for the first time signs of mediastinal pressure — severe difficulties in swallowing and hoarseness. He died 48 hours later.

Treatment consisted in the beginning of supportive measures, such as glucose, saline and amino acid infusions, alkali and antispasmodics. As soon as he was able to retain food, he was given small frequent feedings. After the diagnosis of hypochlorhydria was established, he received dilute hydrochloric acid before meals. The diet was high in carbohydrates and proteins and rich in vitamins. The hypochromic anemia

in the beginning of the illness was combated with iron and crude liver extract. Because of the intermittent type of temperature, the patient was given a course of penicillin, receiving a total of 1,000,000 units intramuscularly in a period of 10 days. This, however, had no effect on the fever. He also received a course of Pentnucleotide (10 cc. intramuscularly three times a day for sixteen injections) because of the leukopenia and neutrophilia. This, too, was entirely unsuccessful. He also received eleven 500-cc. blood transfusions over a period of 2 months. Otherwise the treatment was purely symptomatic and supportive.

Autopsy

At autopsy the right pleural cavity contained 2500 cc. of straw-colored fluid. The right lung was entirely collapsed, and the left lung, as well as the heart, was markedly displaced to the right. At the root of the right main bronchus there was a large tumor mass, measuring 6 by 4 by 2.5 cm. There were also six peribronchial lymph nodes, of pea to bean size, around the root of the right main bronchus. The liver was markedly enlarged, weighing 2020 gm., but the cut surface was normal. The spleen was somewhat enlarged, weighing 280 gm., but showed a normal cut surface. No enlarged abdominal or superficial lymph nodes were found. The sternal marrow appeared to be paler than usual. Microscopical examination of the lymph nodes showed many typical Reed-Sternberg giant cells, and the sternal marrow again was atrophic and fibrotic. The liver showed a mild degree of amyloidosis. The spleen appeared to be normal. Diagnosis: Hodgkin's disease.

Discussion

The data derived from the history of this case, as well as the physical findings and the clinical course of the disease, permitted the diagnosis of Hodgkin's disease, which was later confirmed by autopsy findings. Not until two weeks prior to the patient's death, however, did the clinical picture become clear enough to permit a definite diagnosis of this disorder. Up to that time there were many findings suggesting Hodgkin's disease without being pathognomonic of this disorder. A brief review of the clinical course will demonstrate the diagnostic difficulties in this case.

The prodromal symptoms were related to the gastrointestinal tract. In spite of repeatedly negative x-ray findings, the clinical symptoms were so typical of a duodenal ulcer that the patient's physician felt justified in putting him on an ulcer regime. The fact that Hodgkin's disease may be preceded by gastrointestinal disorders was stressed both by Rolleston[5] and by Bramwell[6] as early as in 1909. In this case the gastrointestinal disorders finally became severe enough to produce a picture of partial intestinal obstruction, for which the patient was originally referred to the hospital. During the first weeks of his hospital stay, the clinical picture was characterized by generalized weakness and loss of weight, so that at one time a diagnosis of pulmonary tuberculosis was considered. This was ruled out, however, by repeated chest x-ray and laboratory examinations.

Although from the etiologic point of view tuberculosis is still favored by some investigators, there is general agreement that, clinically, tuberculosis follows rather than precedes Hodgkin's disease. This position was further strengthened by Ziegler's[4] investigations, showing that in 25 per cent of patients with Hodgkin's disease the terminal picture was that of miliary tuberculosis. According to Jackson and Parker,[3] generalized weakness and loss of weight, for which no cause can be found, are not infrequently the first symptoms and may be most difficult ones to evaluate. The fact that Hodgkin's disease in its initial stage may be marked by the most diverse symptoms and signs was also stressed by Jackson and Parker.

To the prodromal symptoms of gastrointestinal disorders, generalized weakness and loss of weight might be added in this case the hypochlorhydria of the gastric juice and the mild hypochromic anemia, findings that, according to Ewing,[7] are not infrequently noted and may dominate the clinical picture for some time. Fever occurred fairly late in this case. At first it was of the remittent type, without, however, ever resembling the typical Pel–Ebstein fever. Later it became sharply intermittent, suggesting a more or less septic condition. Repeated blood cultures, however, were negative, and a course of penicillin produced no changes.

The blood picture was both bizarre and puzzling. At first there was a mild to moderate hypochromic anemia, which at times showed a tendency toward the pernicious type, but which responded fairly well to liver and iron therapy, as evidenced by the gradual increase in reticulocytes. Whereas the red-cell picture appeared to be reasonably stable, the white-cell count showed a marked leukopenia which continually increased in severity. On several occasions a neutrophilia was also present, which, however, resisted treatment with Pentnucleotide. On two occasions young white cells were also found, but they were not persistent and on subsequent smears were absent. The blood platelets were normal. At no time was there an increase in eosinophilic cells, which some authors, among them Bunting,[8] describe as one of the most significant diagnostic signs in Hodgkin's disease. One week prior to death there was a slight but steady increase in the white cells, whereas the red-cell count dropped markedly. Repeated blood transfusions were ineffective. A smear of the sternal marrow, which is also considered to be a helpful diagnostic procedure, appeared normal and did not clarify the clinical picture.

Other diagnostic procedures, such as complete gall-bladder and kidney studies, as well as x-ray examination of the long and flat bones, agglutination tests and numerous blood chemical tests, revealed normal values.

The physical signs were extremely vague. Except for a progressing hepatomegaly, the findings were practically nil until two weeks prior to death. There was no palpable splenomegaly, except for one occasion when the spleen seemed to be palpable on deep inspiration. Superficial lymphadenopathy was absent during the entire course. The tenderness over the flat bones, especially over the

sternum, and over the splenic region, should, however, be mentioned. Although hepatomegaly is mentioned by many authors as a fairly consistent finding in Hodgkin's disease, the occurrence of spenomegaly and superficial lymphadenopathies appears to be a much more frequent finding both in Hodgkin's granuloma and in Hodgkin's sarcoma and seems to be fairly pathognomonic of these two types, even the mediastinal form (Jackson and Parker,[3] Ewing,[7] Boyd,[2] Cecil[9] and others).

A striking change in the clinical picture appeared two weeks before death. Then for the first time, mediastinal-pressure symptoms occurred, such as atelectasis of the right lung due to compression of the right main bronchus, difficulties in swallowing and hoarseness. This picture appeared to be fairly consistent with that described by other authors as typical of the mediastinal type of Hodgkin's disease. Up to that time, as already mentioned, the clinical picture was characterized by vague protean findings, some of which were suggestive but not pathognomonic of this disorder.

Summary

A case of Hodgkin's disease, mediastinal in type and characterized by an unusual combination of prodromal symptoms and signs, is described, and the clinical course and the laboratory and autopsy findings are discussed.

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MEDICAL PROGRESS

PHYSIOLOGY

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THE re-examination of established principles often proves to be as effective a means of progress as the exploration of new fields. This is especially likely to occur in those instances where the weight of long tradition or great authority and the superficial appearance of reasonableness have combined to discourage the critical analysis of a doctrine. The demand for re-evaluation within recent years of two well buttressed concepts may therefore be viewed as important indications of progress in physiology and medicine. In both, which are discussed in the first two sections below, revision of basic physiologic tenets is involved, along with reconsideration of means of treatment. The first instance concerns the physiologic processes that participate in the production of edema in congestive heart failure, which have required renewed study in the light of revised methods of treatment. The second has to do with clinical observations on the abuses of recumbency and bed rest, which point to the need for more adequate data on the physiologic changes that occur in these circumstances, particularly in the aged and obese.

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Edema in Congestive Heart Failure

The subject of edema in congestive heart failure has been reopened through the examination of the value of restriction of fluid and salt in studies in which the two factors were varied separately.

Schroeder[1] studied 23 patients with congestive heart failure in whom restriction of salt intake to approximately 1.0 gm. daily was sufficient to establish diuresis. When, in these circumstances, water intake was increased, edema was not increased. Occasionally, diuresis increased when added water was taken, and diminished with restriction of fluids. Schroeder concluded that restriction of salt is an important feature of the regime in congestive heart failure, whereas restriction of water is not essential.

Similar conclusions were reached by Proger, Ginsberg, and Magendantz,[2] who gave 4 patients recovering from congestive heart failure 10 to 12 gm. of salt daily in addition to a dietary intake of 5 to 7 gm. Within four to eight days these patients developed a clinical picture indistinguishable from congestive heart failure, which was remedied by digitalis. Three

patients were permitted to increase their fluid intake to 3000 cc. daily without increase in salt intake. In none of these were there any noticeable harmful effects.

Finally, Schemm[3, 4] has shown that water has valuable diuretic properties, and that when water in excess of daily requirements is given, especially when sodium is moderately restricted and an acid-ash diet consumed along with moderate amounts of dilute hydrochloric acid or ammonium chloride, edema and other fluid accumulations disappear and the symptoms of congestive failure are relieved. Edema of other origins appears also to be favorably influenced. Fluid intakes as high as 5000 to 8000 cc. a day have been employed successfully in such treatments. Presumably a high water intake is effective because it provokes an active diuresis, even in badly damaged kidneys, in the course of which excess salt is lost even though the urine is extremely dilute. Reduction in the salt content of the body fluids results in further loss of water to maintain osmotic equilibrium, with the net result that fluid is lost in greater volume than the ingested water.

These studies, which call attention to the role of salt and water accumulation as an important factor in the edema formation in congestive heart failure, also suggest that such accumulations may in fact precipitate the attack of failure. This is confirmed by the recent studies of Warren and Stead,[5] who found that resumption of a normal salt intake and an additional 12 gm. salt daily by two patients who had recovered from failure on a low-salt and diuretic regime led to typical attacks of congestive heart failure. The plasma volume increased prior to the onset of failure, but the venous pressure did not rise beyond the control range. The authors are therefore inclined to view the increased retention of salt and water, followed by an increased plasma volume, as the primary events in the collection of edema, and to discard the conventional theory that the accumulation of fluid results from increased venous pressure, or tissue anoxia, in heart failure.

Evidence that tissue anoxia cannot be responsible for edema formation is presented in another report by the same authors,[6] in which it is shown that the protein content of edema fluid is not abnormally increased, nor is fluid obtained in patients with frank tissue anoxia, whereas the protein content of fluid collected after prolonged elevation of venous pressure is markedly elevated. The accumulation of salt and water is credited, instead, to a deficient renal excretion. This in turn may be due to excessive production of adrenal cortical hormones or to altered renal circulatory dynamics. The latter appears to be the most reasonable. The following sequence of events is then presumed to occur: failure of cardiac output; failure of renal circulation and consequent failure of salt excretion; water retention; increase in capillary pressure as the result of the augmented plasma volume; and consequently, increase in extracellular fluid or edema. The increased venous pressure is this viewed as the *result* of retention of salt and water — not the *cause* of it.

From an *a priori* standpoint this account fails to be completely satisfactory, depending as it does on the establishment of conclusive evidence that plasma volume does in fact increase before venous pressure is raised. It is difficult to accept the suggestion that the heart fails enough to derange the circulation in the kidneys before the venous pressure rises. It is generally assumed that the first reaction of the failing heart is to maintain a normal output through the operation of Starling's law of the heart, whereby the residuum of blood left in the ventricle by an incompletely effective systole is added to the normal diastolic inflow to distend the heart and thus to increase stroke volume to the point where a normal output is maintained at the expense of a slight increase in venous pressure. Failure begins when this mechanism is no longer successful, and increased filling is followed by diminished output. Thus, adding to blood volume in a heart at the point of failure precipitates failure, whereas reducing the volume, as by venesection or pooling of blood behind tourniquets, actually improves cardiac output by reducing the diastolic overload.

Physiology of Rest

Under the stress of an increasing demand for hospital and nursing care, one of the most firmly established of all therapeutic principles is being subjected to critical scrutiny. In the light of this reexamination, the doctrine of rest as a curative measure is seen to have certain important limitations, a number of which are brought out in a recent symposium[7–11] and in subsequent reports.[12–14] The discussion is opened by Harrison, who recalls that John Hunter lived possibly twenty and certainly eight active and productive years after the first symptoms of coronary arterial disease, whereas James Mackenzie survived his initial cardiac attack by seventeen years, during fifteen of which he continued to play golf. He then reviews experiments carried out with Thomas,[15] in which the survival rate was studied in rats after damage was inflicted on the myocardium by burning the left ventricle. In rats whose activity was restricted to approximately 10 per cent of that of unrestricted controls, only 7 survived out of 49, whereas 21 out of 47 survived in the control group. Unconfined rats resumed normal activity in five days, as shown by their optional use of a treadmill in the cage. Forced, strenuous exercise (swimming) failed to influence mortality if it were not begun before forty-eight hours after the cardiac trauma. From these experiments the authors concluded that physical activity within the range of tolerance may be more beneficial than complete rest. They call attention, however, to the obvious fact that restraint, even though it may reduce skeletal muscular activity,

can hardly be termed rest, and it is highly uncertain that the cardiovascular load under these circumstances is in any measure diminished. This may be comparable to the patient who is forced by the physician to maintain an "unhappy recumbency" instead of a "happy sitting." Harrison lists the following as advantages to be sought in prolonged bed rest: a decreased liability to rupture of the heart; a better circulation to the brain during the period of circulatory collapse; and a firmer and smaller scar. The following are cited as disadvantages: the tendency to the formation of pulmonary edema; a diminished circulatory velocity, with a consequent tendency to intravascular clotting; and the development of hypostatic pneumonia, particularly in elderly people.

Levine cites as advantages of bed rest a diminished metabolism, a slower heart rate and a lower blood pressure, all of which diminish the work of the heart or improve its efficiency. On the contrary, the improved venous return associated with recumbency increases the cardiac output by some 25 per cent and tends to counterbalance the gains noted above. It is recognized that attacks of cardiac asthma are more frequent at night after several hours of recumbency, and their victims often learn to overcome them by sitting at the edge of the bed with the feet dependent. By this process, the fluid in the lungs is diminished and the venous blood is pooled in the dependent limbs, thus relieving the overdistended heart and permitting it to contract more efficiently. Even when the patient cannot sit up, it may be possible to carry out both active and passive limb exercises, and to elevate the head of the bed to begin to condition the cardiovascular system for the ultimate resumption of the upright position.

There appears to be general agreement that after surgical operations, particularly those involving the pelvis and abdomen, venous return from the limbs is delayed and serves as the basis for embolus formation in the small veins and venules of the dependent portions of the limbs, particularly in the obese and aged.[16–19] Elevation of the limbs and exercise, especially the latter, markedly decrease the foot-to-carotid-sinus circulation time.[16, 17] Walking soon after operation has been advocated as a measure to minimize postoperative thrombosis. Other advantages of early walking after surgery have been suggested as follows: improved gastrointestinal function, with lessened incidence of abdominal distention; improved muscular strength and absence of asthenia, which lead to a more rapid resumption of full activity; more rapid healing of the wound; improvement in morale; and economy in hospital beds and nursing care and in the cost of illness to the patient.

Dock emphasizes that bed rest is far from physiologic, involving long periods in the dorsal recumbent posture, usually with sedation to suppress the normal tendency to change frequently, and diminished vital capacity and tidal volume. Unless specifically warned against it, the patient will many times a day repeat the Valsalva experiment (taking a deep breath, closing the glottis and contracting the expiratory muscles), when on the bedpan, expelling flatus or moving upward in bed. This maneuver places a great strain on the cardiovascular system, and often causes sudden death after myocardial infarction.

The symposium closes with a discussion of the psychosomatic aspects of rest, calling attention to the fact that the symptom of fatigue is only in rare cases at all related to exhaustion of muscular energy, but rather stems from an inability to direct energy output into properly balanced creative and destructive outlets. Therapy must therefore aim to utilize rather than to blockade the available energy of the patient.[11]

It is obvious that these objections are directed not so much at the doctrine of rest itself as against abuses and misconceptions of the principle. Enforced muscular inactivity does not constitute rest, and may in fact prevent rest. Mental rest is often achieved by a combination of physical activity in a proper environment. Various operations of orthopedic surgery may effectively place a fractured bone at rest without at the same time depressing the functions of nearby joints and muscles. The complete bed rest of the patient with tuberculosis is accompanied by conscious or unconscious psychotherapy aimed at allaying anxiety and arousing a desire to carry out the treatment in every detail.[14] Rest must therefore be prescribed, like any other therapeutic measure, with a clear idea of the aims sought by its employment and of its harmfulness when employed excessively and inappropriately. "Whenever we put a patient to bed," advises an editorial in the British Medical Journal,[20] "we should ask ourselves what we hope to achieve; and it must be something more than a tidy ward, a convenience for examination or a substitute for a convalescent room."

Closely associated is the problem of limitation of exercise in chronic illnesses, such as rheumatic fever, in which the decision may lie between a life of semi-invalidism and a virtually normal existence. Here the report of Kohn and McEldowney[21] may serve as a guide to the extent to which persons with seriously impaired hearts may lead normal lives. The study concerns the fate of 233 former pupils of a special school for children who, because of disease, accident or congenital deformity, could not attend a regular school with "safety and profit." Eighty-five per cent had rheumatic heart disease, and 9.4 per cent suffered from congenital lesions of the heart. Twenty-five per cent had died, and 20 per cent had had recurrences of rheumatic fever. Of 130 pupils re-examined between the ages of seventeen and thirty-three years, only 5 per cent had never worked or were not working at the time of re-examination. Thirty-two women had married, and

of these, 14 had had one child, 3 had had two, and 2 had had four; in no case had the heart lesion affected adversely the pregnancy or labor. Fifty per cent of the women were doing their own housework, and many were performing heavy work.

It is obvious that, despite the seriousness of their heart disease, a majority of the persons included in the study had been able to enjoy, within their limitations, active and productive lives. Whether the mortality within the group would have been any less had their activity been more rigorously curtailed is open to question, but it is probable that the mortality in this group of patients was an indication of the seriousness of the heart disease, and might well have been as great if they had been receiving sanatorium care as semi-invalids during the whole period of the study.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31371

Presentation of Case

A fifty-year-old widowed chauffeur was admitted to the hospital because of progressive anorexia, weakness, malaise and weight loss.

Sixteen years before admission the patient had had an acutely inflamed gall bladder drained. Seventeen days postoperatively he was discharged with a small draining sinus, which had continued to drain creamy yellow to green purulent material up to the time of admission. The drainage was intermittent, with frequent periods of several days during which the sinus tract closed. Within a few days there invariably followed a short period of local discomfort and often pain, which was followed by reopening of the sinus and profuse drainage for a few days. Approximately one year after the operation, while doing heavy work, an orange-sized hernial mass suddenly appeared at the site of the operative scar. This hernia had never been painful and had not increased in size. Five years before admission he had had "pneumonia," which was treated at home. The patient had otherwise been entirely well until about two years before entry, when he began to feel sluggish, had no energy and lost ambition and interest in his work. He began to lose his appetite and weight. One year before admission he began to have mild attacks of "asthma," which became worse; two months before admission he was admitted to another hospital because of a severe attack. There had been no hemoptysis. He was discharged after eleven days, feeling considerably improved. Since that time he had continued to grow weaker and more exhausted. He had had occasional night sweats for an undetermined period of time.

Twelve years before entry his wife died after sanatorium care for tuberculosis of the sacroiliac joint. An eighteen-year-old daughter was living and well.

As a youth he had worked for several years in a dusty cardboard-box factory. Two years before admission he had worked for several months in a boiler room shoveling soft coal. He had had a mild chronic "cigarette cough" for about ten years, which im-

*On leave of absence.

proved when he stopped smoking three months before entry.

Physical examination revealed a poorly nourished, well developed, pale man with signs of recent weight loss. There was no lymphadenopathy. The chest was barrel shaped and showed diminished expansion. There were moderately fine rales at both bases posteriorly, extending higher on the right side. In the axillary line bilaterally there were some high-pitched musical rales. The heart border was not percussible, but the heart sounds were of fair quality. A blowing Grade 2 apical systolic murmur was heard

The temperature was 98.6°F., the pulse 115, and the respirations 20. The pulse soon returned to about 90. The blood pressure was 100 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,000,000, with 80 per cent hemoglobin, and a white-cell count of 10,700, with 74 per cent neutrophils, 12 per cent lymphocytes and 14 per cent monocytes. The urine was acid, with a specific gravity of 1.015, a trace of bile and a rare white cell. A sputum specimen showed no tubercle bacilli. The stool was brown, and guaiac tests were positive.

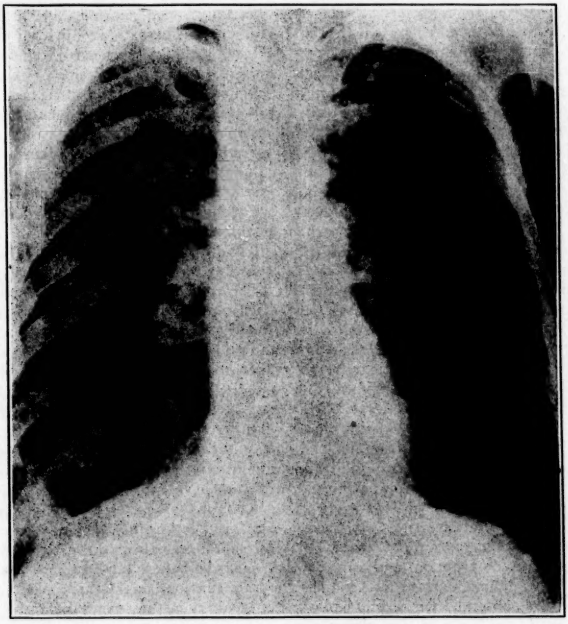

FIGURE 1. *Roentgenogram of Chest.*

but was not transmitted to the axilla. The abdomen was scaphoid, with an old operative scar in the right upper quadrant. At each end of the scar was a depression, the lower one having some dried exudate around it. To the right of the scar opposite its midportion was a firm movable mass in the abdominal wall; this could not be reduced. On coughing, other viscera herniated into the pouch and lodged beside the permanent mass. Distinct epigastric tenderness and spasm were more marked on the right than on the left. No other masses were felt. One observer noted right costovertebral-angle tenderness.

Tuberculin tests in dilutions of 1:100,000 and 1:10,000 were negative. A blood Hinton test was negative.

X-ray films of the chest showed both lungs to be involved in a grossly nodular process, with a network of increased density connecting the more miliary nodules (Fig. 1). In addition there were areas of emphysema in the right lower lung and a few rarefactions suggesting cavities in the upper lung fields, particularly on the right. The heart was small but otherwise not remarkable. An electrocardiogram was consistent with coronary heart disease.

The serum nonprotein nitrogen was 36 mg. per 100 cc. with subsequent lower values, and the total protein 7.8 gm., with an albumin-globulin ratio of 0.88; the chloride was 98.0 milliequiv. per liter, and one week later 85 milliequiv. The prothrombin time was 30 seconds (normal, 18 to 20 seconds). An oral Graham test was tried but the dye failed to pass the pylorus and outlined a distended stomach.

The patient was extremely weak and constantly tired. On the fifth hospital day the temperature became elevated and remained between 100 and 102°F. for four days. Thereafter for about a week the oral temperature was between 97 and 98°F. On the sixth day he had an episode of what was thought to be paroxysmal auricular tachycardia, with a pulse rate of 160, which reverted to normal rhythm spontaneously in about twelve hours. A gastrointestinal series on the sixth hospital day revealed a normal esophagus. The stomach was atonic and contained fluid and retained food. Fluoroscopically there was thought to be a shallow ulceration on the lesser curvature just below the angulus. After transient prepyloric spasm the duodenal cap filled out well and appeared normal. The upper small intestine was not remarkable. The diaphragm moved equally well on both sides. Two days after the gastrointestinal series a gastric lavage yielded large amounts of barium. At that time numerous rales were heard throughout the chest and the patient stated that the lavage made him short of breath. A sputum culture was negative for beta-hemolytic streptococci and pneumococci.

On the eleventh hospital day the patient began to cough up blood-tinged sputum and a few particles of what appeared to be necrotic tissue. Frequently repeated smears for tubercle bacilli were negative, and a pathological examination on the sputum sediment revealed no tumor cells. A gastroscopy on the fifteenth day showed superficial gastritis with multiple erosions. The patient was relieved by daily gastric aspirations after the twentieth hospital day. He then appeared to have repeated attacks of pyloric obstruction, and approximately 1000 cc. of foul-smelling, dark-brown, guaiac-positive, thick fluid was obtained with each aspiration. On the twenty-first hospital day the temperature, pulse and respirations began to rise, the temperature fluctuating between 100 and 103.5°F.

On the twenty-second day the patient became markedly dyspneic and apprehensive. The abdomen was distended. Peristalsis was present. The spleen was not felt. The liver was thought to be large. The blood chloride was 77 milliequiv. per liter, and the total protein 4.5 gm. per 100 cc. A van den Bergh test was 0.9 mg. per 100 cc. direct, and 1.2 mg. indirect. On x-ray examination the appearance of the chest had not changed appreciably.

The patient became progressively weaker, more dyspneic and ashen-gray despite an oxygen tent. His lungs were filled with rales, and he expired on the twenty-fifth hospital day.

Differential Diagnosis

Dr. John W. Cass: The initial statement in this man's history makes one think of cancer of the stomach more than anything else. If cough were added, one would think of tuberculosis. The postoperative story is that of a patient with a residual empyema of the gall bladder, a draining sinus and the subsequent development of a ventral hernia. The history indicates a transition into a progressive illness, with localization in the chest as well as in the abdomen. The asthma by itself is not significant, since it could have been a symptom of a general disease. A malignant lesion of the chest is not uncommonly ushered in by attacks of asthma, and tuberculosis is not infrequently accompanied by asthmatic attacks.

We learn that there was a family history of tuberculosis, which suggests that perhaps the whole story was accounted for by tuberculosis. Contact is the one thing that one searches for, and here it can be established.

I know of no occupational hazard connected with a cardboard-box factory or with shoveling soft coal.

The physical examination again localizes the disease to the chest and to the abdomen. It brings into the picture a mass, which was not the hernia and which was not related to the sinus tract. The laboratory work indicates an obvious secondary anemia. The blood smear showed 14 per cent monocytes, which is not helpful by itself but is suggestive of tuberculosis. The trace of bile in the urine we have to accept as a pathological finding that incriminates the liver. The tuberculin tests are interesting. Negative tests with dilutions of 1:100,000 and 1:10,000 are rare in an adult of fifty, but in these dilutions they cannot be considered negative. The test should have been done with a dilution of 1:100. A negative tuberculin test in a man of this age is so rare that one might suspect he had some form of tuberculosis in the terminal stage.

May we see the x-ray films?

Dr. George W. Holmes: There are two obvious things in this man's chest. He has a wide anteroposterior diameter and a low diaphragm — the characteristic appearance of an emphysematous chest. In addition he has a diffuse process that involves both lungs, the right more than the left. There is a suggestion of a cavity in the right apex. It is not definite enough, however, for me to say that it is a cavity; so that I am not particularly helpful. If it is a cavity, we have to consider carcinoma, tuberculosis and silicosis, although I should think that the last was unlikely.

DR. CASS: The x-ray report says "miliary nodules." Are they nodules or tiny cavities?

DR. HOLMES: I suppose they meant small nodules. I do not recognize that as a customary expression.

DR. CASS: Are they blebs or cavities?

DR. HOLMES: I do not know. Part of the chest is blurred, but there is probably some fluid in the pleural cavity.

DR. CASS: In the lateral films is there any evidence of bone change?

DR. HOLMES: No.

DR. CASS: There was a gastrointestinal series mentioned in the protocol.

DR. HOLMES: The films are not helpful.

DR. CASS: There was a statement about prepyloric ulceration.

DR. HOLMES: I think that we have to take that for what it is worth. I am not able to demonstrate anything on the films. It was a fluoroscopic note.

DR. CASS: So the x-ray picture is that of a nodular, miliary process, not one of small cavities. The presence of a large cavity is questionable. The likeliest diagnosis is tuberculosis or a malignant neoplasm, pneumoconiosis or sarcoid being rather poor bets.

The nonprotein nitrogen was normal, which is surprising in a man so ill. The total protein was high and the albumin-globulin ratio was low when he came in. Later, the low protein and increased prothrombin time suggest intrinsic liver damage.

The paroxysmal auricular tachycardia does not help. There is no evidence that we are dealing fundamentally with a heart condition. Dr. Holmes says that we have to accept the statement that there was a gastric ulceration, but the most information we get is that there does not seem to have been any gross intrinsic disease of the stomach. There was ulceration, but it was not characteristic enough to make one think of tumor.

A real but unsuccessful effort was made to find acid-fast organisms. There was no evidence of tumor cells, at least in a single specimen. Gastroscopy helps in making us think that we are dealing, so far as the abdomen is concerned, with obstruction of the stomach. It could have been due to a pathologic process close to the pylorus or it could have been secondary to the hernia. In general the abdominal situation seems more compatible with tumor than with tuberculosis.

In the terminal days of the patient's course there was a marked change in the blood chemical findings, which is again compatible with a good deal of intrinsic liver disease. But we are dealing with a patient with extreme debility and malnutrition, and the laboratory work may not be too significant. It is important that there was no significant change in the x-ray films of the chest.

In summing up the situation, it seems to me that the picture is that of a wasting disease with localization both in the chest and in the abdomen, and that in the beginning the difficulty was chiefly in the liver. So far as the chest is concerned, there was a diffuse nodular miliary process. The tuberculin test was negative, at least in dilutions of 1:10,000, as were sputum studies, so that the process in the chest is more compatible with tumor than with infection. I did not mention actinomycosis. That does give a nodular appearance, but it seems to me that the evidence narrows down to tuberculosis or tumor. So far as the abdomen is concerned, there were positive findings of gall-bladder empyema, with a draining sinus, a large liver, no jaundice and laboratory studies indicating a good deal of intrinsic liver damage. The pyloric obstruction, so far as we can tell, was extrinsic and could have been due to pressure from a mass in the region of the gall bladder or bile ducts. There may have been a rupture of the abdominal process into the chest, so that from a diagnostic point of view, we have to decide, first, whether we are dealing with tumor or infection and, second, whether there were two diseases.

It seems to me that if we can logically connect the two it is safer to make one diagnosis than to make two, and the weight of evidence seems to me to be in the realm of a malignant tumor. If so, where did it lie? We know that in patients with chronic draining sinuses for this length of time malignant degeneration is liable to develop in the sinus tract or gall bladder. Malignant disease in these areas usually metastasizes to the chest. If the process in the chest was nodular, it is compatible with metastatic malignancy, although one cannot rule out tuberculosis, particularly that of the miliary type. By far the safest diagnosis is malignant tumor developing in the region of the gall bladder, with metastases to the liver and lungs.

A PHYSICIAN: Would someone comment on the low chloride?

DR. FRIEDRICH W. KLEMPERER: It was probably due to the vomiting, with consequent loss of chloride.

DR. E. FREDERICK ALSTON: I should like to ask about the significance of the elevated monocyte count. Does this occur with many types of prolonged illness?

DR. CASS: There is a pouring out of monocytes in many types of infection, such as undulant fever and tuberculosis. A single reading of that number, however, does not help me in the diagnosis one way or another; it does, however, suggest tuberculosis.

CLINICAL DIAGNOSIS

Carcinomatosis.

DR. CASS'S DIAGNOSIS

Carcinoma of gall bladder, with metastases to liver and lung.

Anatomical Diagnoses

Acute pulmonary tuberculosis (miliary).
Adenocarcinoma of head of pancreas, with metastases to regional lymph nodes, stomach, liver, abdominal wall and lungs.
Tumor thrombi in lungs and liver.
Tuberculosis of bronchial lymph nodes.
Pleuritis, acute fibrinous, with effusion.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy on this man showed a bizarre picture in the lungs. There was 300 to 400 cc. of turbid fluid in each pleural cavity. Both lungs were replaced by yellowish miliary areas of necrosis, some of which were confluent and frankly caseous. Many of the blood vessels were plugged with grayish-white material that looked like tumor thrombi, and this was confirmed microscopically by frozen sections. In the head of the pancreas, just away from the common duct, was a firm granular grayish-white mass, 4 cm. in diameter, which was the primary tumor. The liver was riddled with tumor, which had replaced from one third to one half the parenchyma. Here also, as in the lungs, the blood vessels were involved, and the portal vein radicals within the liver were filled with tumor thrombi. Our final sections of the lungs showed that in addition to the carcinoma there was true caseation, and stains for tubercle bacilli showed myriads of organisms. It is almost inconceivable that they were not found in the sputum, since they could be picked out in our sections even under low power. We were unable to find tuberculosis in the sinus tract of the old scar. There was a large tumor nodule beneath the scar, which was a metastasis to the abdominal wall. The tumor proved to be an adenocarcinoma. There were metastases to the regional nodes around the pancreas, some of which had infiltrated the wall of the stomach; so far as we could tell these had not broken through the mucosa, although a number of superficial mucosal vessels containing small bland thrombi were eroded. There was some blood in the stomach, but we could find no evidence of tumor. I imagine that the pressure of the metastatic nodules on the vessels had caused the thrombosis and the subsequent erosion.

CASE 31372

Presentation of Case

A seventy-six-year-old widower was admitted to the hospital because of urinary frequency and nocturia.

During the previous six months, overflow dribbling had progressed to spontaneous and uncontrollable voiding, and during the two days before entry he was able to void only a few drops at a time. There had been no pain, hematuria or previous acute retention.

He had had no venereal disease and no other serious illness, except for typhoid fever about four years before entry.

Physical examination revealed a well developed, well nourished man who appeared well and in moderately severe distress after catheterization. The teeth were in poor repair, and there had been many extractions. The lungs were clear and resonant, with normal breath sounds. The heart was not enlarged. The rate and rhythm were normal, and no murmurs were heard. Examination of the abdomen was negative, except that the liver edge was approximately two fingerbreadths below the right costal margin. A rectal examination revealed an enlarged prostate. The median sulcus was present, and the right lobe felt smooth, soft and about two times the normal size. The left lobe was considerably more prominent than the right, measuring approximately 5 by 3.5 cm., and was quite firm and rubbery. A tense, somewhat fluctuant 1-cm. mass was palpated on the lateral aspect of the left lobe. The extremities were negative.

The temperature was 100.5°F., the pulse 80, and the respirations 20. The blood pressure was 140 systolic, 75 diastolic.

Examination of the blood showed a white-cell count of 7000 and a hemoglobin of 75 per cent. The serum protein was 5.3 gm. per 100 cc., the acid phosphatase 1.4 units, and the alkaline phosphatase 1.6 units. The nonprotein nitrogen was 34 mg. per 100 cc., and the phosphorus 2.4 mg. A blood Hinton test was negative. A catheter specimen of urine was grossly bloody, with a specific gravity of 1.024, and gave a ++++ test for albumin. Urine cultures showed *Staphylococcus aureus*, and three consecutive blood cultures yielded *Staph. aureus*; all the blood-culture strains were coagulase positive. The organism was found to be penicillin sensitive.

On the second hospital day the patient was cystoscoped. The mucosa was red and edematous. The median and both lateral lobes of the prostate were large and projected into the bladder. The testes were normal. The right vas deferens was slightly thicker than the left, and the globus minora of the right epididymis was swollen, tense and extremely tender. On the third day penicillin therapy was begun, and on the fourth day a suprapubic cystostomy was performed. The temperature, which had been spiking daily to 103°F., returned to normal; the pulse, which had been between 90 and 110, became normal on the fifth day; and the respiratory rate, which had risen to 45 on the third day, returned to 20. The white-cell count rose to 13,400, and the hemoglobin to 85. On the sixth day the nonprotein nitrogen was 60 mg. per 100 cc. From the fourth to the ninth day the patient appeared much better and progressed favorably in preparation for a prostatectomy.

During the forenoon of the ninth day he had a sudden chill. The rectal temperature rose to 103.5°F. but returned to normal in four hours. The pulse rate was elevated to 110, and the respirations rose to 40. That evening there was slight edema of the ankles. There was moderate dyspnea, and moist crackling rales were heard at both bases. There was no pleuritic pain or signs of consolidation. A loud rough systolic murmur lasted throughout systole; it was heard over the entire precordium but was loudest over the apex. A precordial thrill was felt. X-ray examination on the following morning showed indistinct heart borders due to considerably increased density that extended throughout both lung fields, radiating from the hilar areas into the lungs; this was most marked in the lower lung fields. The density appeared to follow the vascular markings. A small amount of fluid was present in the pleural sinuses. No evidence of infarcts was seen.

On the ninth day the serum nonprotein nitrogen was 42 mg. per 100 cc., and the protein 5.3 gm. On the tenth day digitalization was begun. Late that afternoon the patient complained of a vague chest pain. In the evening he experienced sudden distress. He became more dyspneic, orthopneic and cyanotic. He insisted on sitting on the edge of the bed and had a sensation of impending doom. The peripheral pulse was extremely weak, and the skin cool and clammy. The pain in the chest radiated down both arms, and the dyspnea became rapidly severer. The chest was full of loud moist rales, and the heart sounds were distant and irregular. Within thirty minutes of the onset of the distress he expired.

Differential Diagnosis

Dr. Paul D. White: The urinary difficulties indicate prostatic obstruction. I am not able to relate the typhoid fever to the present story.

This man apparently had a normal heart at the time of entry into the hospital, so far as one can tell from the physical examination. The liver edge was approximately two fingerbreadths below the costal margin, but that was probably due to a low position rather than to enlargement. The prostate was firm and rubbery, apparently not so hard as would be the case in cancer. The fluctuant mass suggests an abscess, of course. The urinary findings seem to be in keeping with prostatic enlargement and infection. The acid phosphatase is within normal range, but that does not rule out cancer of the prostate. Only an increased acid phosphatase would suggest cancer and that is not the case here.

Were any blood cultures taken after penicillin therapy was begun?

Dr. Benjamin Castleman: The last blood culture, taken on the fourth hospital day, was positive.

Dr. White: And penicillin was given on the third day and continued thereafter. I note that a chill occurred despite the penicillin. How much was given?

Dr. Castleman: Ninety-six thousand units a day.

Dr. White: In divided doses, not by drip? That is an important point.

Dr. Castleman: He was given 12,000 units every three hours.

Dr. White: I wonder why he had an elevation of the nonprotein nitrogen. Perhaps it was due to renal involvement. The clinical appearance was in keeping with the drop in temperature, pulse and respirations, despite the elevated white-cell count.

This patient, who previously had shown no murmurs or thrill, abruptly developed an unusual cardiac murmur and thrill. I wonder how loud the murmur was. We have had a successful experience in the last year or two, largely owing to close contact with Dr. Samuel A. Levine when re-examining Army cases, with the classification of heart murmurs from Grades 1 to 6. This murmur might have been the type that one can hear with the stethoscope actually off the chest, that is, Grade 5 or 6. It was at any rate a significant murmur.

Are the x-ray films here?

Dr. C. Hale: All the pulmonary vascular markings are prominent, and there is also a diffuse haziness.

Dr. White: There are no areas suggesting infarction or consolidation?

Dr. Hale: I do not see any.

Dr. White: The heart is not particularly enlarged. The aorta looks all right for a man of seventy-six.

The nonprotein nitrogen came down terminally, and therefore the patient did not die of uremia. Digitalis was begun the day after the acute complication arose. On the basis of the x-ray findings, it was evidently thought that digitalis was needed. The patient had pain for the first time on the tenth day. The acute illness on the ninth day was not accompanied by pain, — at least there is no statement about it, — but there were dyspnea, a chill and edema of the ankles and lungs. Where was the distress that he suffered on the evening of the tenth day, which was evidently much severer?

Dr. Castleman: Chest pain is all that is recorded.

Dr. White: A sense of impending doom is not a reliable symptom in patients who have heart trouble. Nervous persons with simple paroxysmal tachycardia may have a sense of impending doom, whereas people actually dying usually have no such sense. Still, the symptom may be significant here, for he was extremely sick and we may judge by inference that the pain or distress was severe.

In review there are several things that seem clear. Whether there was a prostatic tumor, I do not know; I doubt it. The prostatic infection, possibly retrograde to the bladder and kidneys, was present to start with, and following that came a *Staph. aureus* septicemia, which in turn was followed by acute heart failure.

The episode on the ninth hospital day was at-

tended by what sounds strongly suggestive of mitral regurgitation of an unusual nature, probably the result of rupture of a mitral valve cusp or chorda tendinea, secondary to acute bacterial endocarditis. Such a thing could have happened in the course of a week or two, the endocarditis having been silent for a while. Endocarditis due to *Staph. aureus* infection is, as a rule, extremely severe and rapid in its course. Other causes of such a murmur with thrill seem less likely. Dilatation of the left ventricle, without structural change, under the stress of illness of any sort may give a murmur, but it is not so pronounced as the one that was found here.

Perforation of the ventricular septum from infection might have occurred, but one would expect that the murmur and thrill would have been nearer the sternum than they were. A rapidly developing aortic stenosis, with large vegetations, should also be mentioned as a possibility but not a probability. Metastatic carcinoma involving the heart is less likely than infection. Complicating septic infarcts of the lungs must be considered, but the electrocardiographic findings do not favor an acute cardiac strain (cor pulmonale) from that source. Thus, bacterial endocarditis, with rupture of a valve cusp or chorda, best explains what happened on the ninth day.

On the tenth day something else happened that precipitated death. This sounds like an acute coronary occlusion, which caused death in half an hour. He had severe chest pain radiating down both arms, with collapse. Pulmonary embolism is unlikely. Coronary atherosclerosis is the most frequent cause of coronary occlusion, but it is more intriguing, of course, to try to fit the picture into one piece. Hence I suggest the possibility, or indeed the probability, of acute coronary embolism due to vegetations on either the mitral or aortic valve. Dissection of the wall of an infected aorta and rupture of the heart wall itself from abscess, with cardiac tamponade, should be mentioned as diagnostic possibilities but they are not likely.

I will stand on the diagnoses of prostatic abscess, *Staph. aureus* septicemia, acute heart failure secondary to acute bacterial endocarditis with rupture of the mitral valve or one of its chordae and, finally, acute coronary embolism.

DR. CASTLEMAN: Dr. Smith, you saw this man, would you like to comment on the urinary infection?

DR. G. GILBERT SMITH: The only thing that occurs to me is that he might have had an abscess in the left lobe of the prostate.

DR. CASTLEMAN: Dr. Segall, have you anything to add?

DR. HAROLD SEGALL: One interesting possibility is that the murmur might have occurred as a result of infection, or infarction, of the myocardium with involvement of the papillary muscle and rupture there. Cardiac rupture frequently starts at the base of the papillary muscle. In the course of twenty-four hours extension proceeds from the base of the papillary muscle until it reaches the pericardium; this sometimes happens in half an hour.

DR. WHITE: But he had no pain.

DR. SEGALL: In old people it may start silently, and the first thing you know the heart has ruptured.

CLINICAL DIAGNOSES

Benign prostatic hypertrophy.
Coronary thrombosis.

DR. WHITE'S DIAGNOSES

Prostatic abscess.
Septicemia (*Staphylococcus aureus*).
Acute bacterial endocarditis (*Staph. aureus*).
Ruptured cusp or chorda tendinea of mitral valve.
Acute heart failure.
Terminal acute coronary embolism.

ANATOMICAL DIAGNOSES

Acute bacterial endocarditis, with mycotic aneurysm of aortic valve and rupture of commissure between right and left posterior cusps.
Adenocarcinoma of prostate.
Pylonephritis, mild: left kidney.
Abscess of epididymis, right.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the commissure between the right and left posterior aortic cusps was an ulcerated granular thrombosed vegetation that had produced a rupture of both cusps (Fig. 1). This ulceration had extended through the commissure as a small mycotic aneurysm, 1 cm. in diameter; this had involved the myocardium of the right wall but had not perforated through the endocardium. Perhaps if the patient had lived a few days longer it might have perforated. Each of these cusps had a frayed edge, so that there must have been free regurgitation.

DR. WHITE: Was the mitral valve all right?

DR. CASTLEMAN: Yes.

DR. WHITE: The murmur must have been diastolic, not systolic. The record fooled me.

DR. CASTLEMAN: There was no involvement of the coronary arteries, unless perhaps a bit of the vegetation on a cusp might have partially covered one of the coronary mouths. It would have had to extend into the right coronary orifice, and at the time of autopsy this was free of disease.

DR. WHITE: How do you explain the final episode?

DR. CASTLEMAN: There is only one way that I can think of. Perhaps one cusp frayed on one day and the other on another day.

DR. WHITE: But there must have been a diastolic murmur, with a diastolic thrill. The examiner obviously timed the murmur wrongly.*

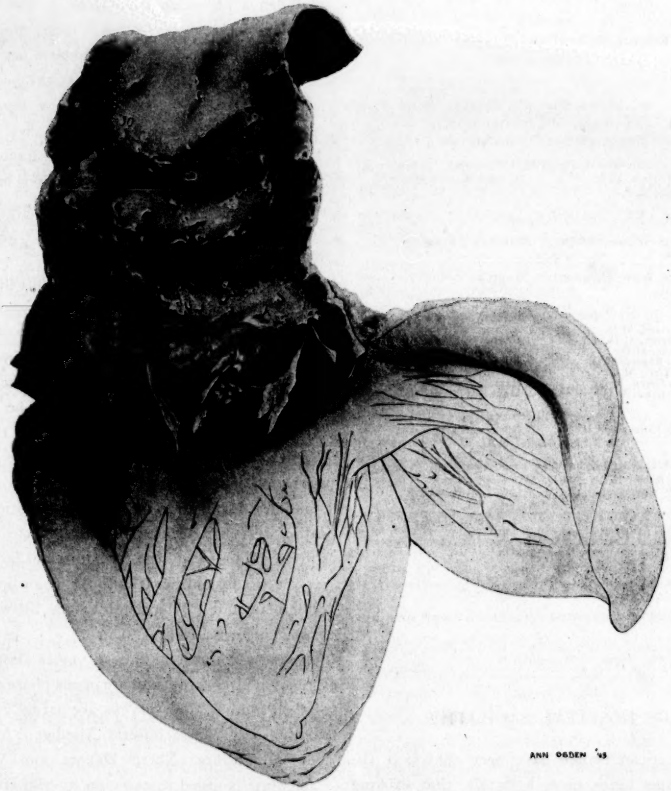

FIGURE 1.

DR. SEGALL: That could happen if the rate was rapid.

DR. WHITE: If there was free aortic regurgitation without aortic stenosis there must have been a predominant diastolic murmur, owing to flapping of these torn cusps in regurgitation. Do you not agree, Dr. Segall?

DR. SEGALL: Yes.

DR. CASTLEMAN: There was no real stenosis.

The remainder of the heart was negative. The prostate was enlarged and quite hard. Microscopically it proved to be an adenocarcinoma. There was an abscess in the right epididymis, and mild pyelonephritis on the left.

*Examination of the record revealed no checkup of the timing of this murmur by internists on the hospital staff. Rupture of an aortic cusp always causes a diastolic murmur, whereas rupture of a mitral cusp or chorda causes a systolic murmur.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

SURVEY OF HOSPITAL FACILITIES

The American people have been told that the United States needs more hospitals, that existing hospitals in many localities need more beds and that large sections of the country are without adequate hospital service. The reports on which these statements are based have been compiled by various organizations, including the American Public Health Association, and although the facts that they present are undoubtedly correct, the conclusions drawn are open to question.

A lack of hospital facilities, where it exists, is linked in almost every instance with a similar lack of medical service: that is, the absence of hospitals deters doctors from practicing in those areas, and vice versa. There is no use in having hospitals without competent doctors to staff them. The two must be correlated.

When a physician is confronted with a medical problem he first collects his facts, weighs them, makes his diagnosis and then determines the course of treatment. That is just what the people of the United States want to have done regarding the hospital and medical situation in their respective states. Furthermore, they wish to have this done on a local or state basis, because they believe that their respective states are too big to be satisfactorily treated by a single prescription, even though they desire a co-ordinated national plan.

With this in mind and through the efforts of the American Hospital Association, the Commission on Hospital Care was established last year, being supported by grants from the Commonwealth Fund, the W. K. Kellogg Foundation and the National Foundation for Infantile Paralysis. The objectives of this commission are to take a census of the present hospital and public-health facilities in the Nation, to appraise their capacity for service, to establish standards for evaluating physical facilities, organization and management of hospitals, to determine the overall national need for additional facilities and service, to formulate a national, co-ordinated hospital plan and to suggest methods by which that plan can be realized.

National interest in this survey is already widespread. Thirty-five states are in one phase or another of their studies, and surveys are actually in operation in Iowa, Massachusetts, Michigan, Minnesota, New Hampshire, North Dakota and Wisconsin. Each state is urged to carry on its own study, since in this way local interest will be aroused, each state will become aware of its need, and a desire to furnish adequate service will be stimulated. The commission will act as a co-ordinating body and will furnish a standard questionnaire, as well as technical consultants, for the use of all states making the survey. The final job of tabulation will be done by the commission's staff.

In Massachusetts, Governor Tobin has appointed a committee, headed by Dr. Vlado A. Getting, Commissioner of Public Health, to carry on the survey. A budget has been submitted and will probably be

approved by the Legislature. Certain hospitals have been asked to fill out the standard questionnaire, to gain experience before submitting it to all hospitals.

The efforts of the Commission on Hospital Care, operating on a voluntary basis in true democratic fashion and supported by private funds, bid fair to be supplemented by the passage of a bill (S. 191) now before Congress, which would amend the Public Service Act "to authorize grants to states for surveying their hospitals and public-health centers and for planning construction of additional facilities; and to authorize grants to assist in such construction." If passed, the bill would immediately provide $5,000,000 to assist state surveys and would allocate $100,000,000 available on June 30, 1946, for the construction of public and other nonprofit hospitals. These two sums could be appropriated each succeeding fiscal year for the same purposes, as determined by Congress. The Surgeon General of the United States Public Health Service would be authorized to make such regulations as are necessary to administer the bill. He would consult with the Federal Advisory Council, consisting of himself, as chairman *ex officio*, and eight members appointed by the Social Security Administrator. States applying for assistance would be required to designate a single state agency as the sole means for carrying out such purposes, provide a state advisory council, meet standards prescribed by the Surgeon General and approved by the Federal Advisory Council and agree to make reports as requested by the Surgeon General. If these requirements are complied with, allotments both for surveys and for construction would be based on the respective state population and financial need, ranging from 25 to 75 per cent of expenditures. Incidentally, essentially the same provisions are included in the Wagner–Murray Bill (S. 1050).

The present situation is that state surveys of hospital and public-health facilities are being encouraged and aided by the foundation-supported Commission on Hospital Care. They may possibly be financially aided by the federal government. In any event, knowledge of hospital needs and what is to be done about them should be materially advanced.

THE EPIDEMIC OUTLOOK IN EUROPE

Disease and pestilence have always been known to flourish during large wars, to follow in their wake and to add to their ravages. Fresh in the minds of many of us are memories of the great pandemic of influenza that occurred near the end of World War I, of the great toll taken by the epidemic of typhus fever that spread through the Balkans during and after the war and of the other widespread epidemics in eastern and southern Europe that followed it. Although tremendous strides have been made in the prevention of disease in the American armed forces and in those of some of our allies, the outlook for serious epidemics among the European populations in the near future is gloomy. Such is the conclusion arrived at by Knud Stowman* in an analysis recently published by the UNRRA.

Several important factors have led to this pessimistic attitude. When the war came to an end, the civil administrations in most of the countries that are likeliest to be affected were in a fluid state and many of them are apt to be so for some time to come. Even more significant are the mass migrations that gained momentum during the latter phases of the war and still continue. The displaced persons include war prisoners, refugees, slave laborers and those who survived the horrors of the concentration camps. Not only are most of these persons in a condition that makes them highly susceptible to epidemic diseases, but they constitute a serious reservoir of infections, which they will carry back to the native lands to which they are repatriated.

Some of the most dangerous diseases that it is feared may be introduced into previously unaffected areas have already made their appearance to a varying extent in the Mediterranean area, the Near East, North Africa and Dakar. They include plague, smallpox and typhus fever. Yellow fever and cholera have thus far shown no tendency to spread, although an outbreak of the latter disease has been recently reported among the natives in Chungking. On the other hand, the more commonly occurring infectious diseases, such as cerebrospinal meningitis, poliomyelitis, typhoid fever, dysentery, diphtheria and scarlet fever, have all shown a twofold or threefold increase during the war years. This is

*Stowman, K. Epidemic outlook in Europe. *Brit. M. J.* 1:742-744, 1945.

apparently a greater increase than was observed in World War I. Furthermore, the incidences of some of the endemic diseases, such as malaria, syphilis, gonorrhea and tuberculosis, have increased many-fold and at a greater rate than that during the previous war.

Dr. Stowman believes that the absence of any real disasters thus far is due, in part, to the low endemic levels of disease in the years immediately preceding the war. The rapid increases in these diseases during the war, he thinks, serve as an index of what may be expected. The vast destruction of homes, especially in the densely populated cities, together with the great population shifts, when added to the increased prevalence of the common infectious and endemic diseases, makes the outlook for large epidemics in Europe even darker than it was after the last war. The only encouraging feature, which tends to offset those fears somewhat, is the fact that we are now better equipped to prevent and cope with some of these problems. In addition, our knowledge of existing situations is far more complete. Dr. Stowman concludes his analysis with the following pertinent remarks:

> On the public health front, World War I lasted not four but more nearly ten years. However, it was gloriously won. Many years of effort in combating infectious diseases have once more been lost so far as Europe is concerned. To make up for backsliding will take several years after the cessation of active hostilities, but the public health profession and services can win their war now as then.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

BARTLEY — John J. Bartley, M.D., of Lawrence, died June 16. He was in his seventy-fourth year.

Dr. Bartley received his degree from Harvard Medical School in 1901. He was Lawrence city physician from 1908 to 1909 and supervisor of school physicians there at the time of his death. He was a member of the Lawrence Medical Society.

His daughter survives.

MEDICOLEGAL ABSTRACT

Medical Schools: What standards are to be used in granting approval; adoption of AMA standards. In a recent decision in the New Jersey Supreme Court the action of the New Jersey State Board of Medical Examiners in passing on the application of a graduate of Middlesex University School of Medicine of Massachusetts for licensure was considered.

The graduate, who had been licensed to practice medicine in Massachusetts, sought to compel the State Board of Medical Examiners to license him to practice in New Jersey by virtue of his license to practice in Massachusetts or, in the alternative, to admit him for examination for license in New Jersey. The application was denied because the applicant had not met the statutory requirement by graduation from a medical school approved by the State Board of Medical Examiners.

The court said in part:

> The question to be determined is whether the respondent is justified in classifying Middlesex University School of Medicine as an institution which was not in good standing. It appears that it bases its conclusion in the grading and standing of medical schools on the standard adopted by the Committee of Education of the American Medical Association and makes public the names of the schools which it approves. It is argued by the relator that the action of the respondent in accepting the grading of medical schools by the American Medical Association is without using its own judgment or discretion but constitutes an unlawful delegation of its duty and power. We think not. It is entirely within its discretion, it seems to us, to adopt the standard and grading of an organization of which it has knowledge and confidence. We think it acted within its sound discretion within the meaning of the statute *supra* and was not actuated by arbitrariness or capriciousness. — (*Rothseid* v. *State Board of Medical Examiners*, 132 N. J. L. 38, 38 Atl. 2nd 444 [1944].)

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PLANS FOR A NEW DENTAL DIVISION

A division of dental health in the Massachusetts Department of Public Health will be created on July 1, 1946, subject to legislative approval of funds for the new division.

It is planned that Lieutenant Colonel Francis B. Carroll, of Waban, will become director of the division. Dr. Carroll is at present with the First Service Command. Prior to that he was with the Department of Public Health as district health officer in the Pittsfield area.

The director and assistant director will be centrally located in Boston and will have technical supervision over dentists and dental hygienists attached to the district offices.

The objectives of the division will be to stimulate more effective dental care of preschool and school children through official and voluntary agencies, to initiate educational projects in dental health in schools, service clubs and other organizations, to assist in special field studies and to inspect dental clinics.

Dr. Carroll graduated from Tufts Dental School and then took postgraduate work in public health at Harvard. After attending medical school at the University of Rochester he engaged in full-time public-health work with the Kellogg Foundation in Michigan, later becoming district health officer with this department. For several years he practiced dentistry in Whitinsville, where he specialized in children's work.

(*Notices on page xix*)